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# Reducing the Occurrence of Postpartum Hemorrhage: Controlled Cord Traction Vs. Physiologic Management During the 3rd Stage of Labor

## Abstract

**Background:** Post partum hemorrhage (PPH) is a major cause of maternal mortality worldwide, accounting for approximately 100 000 deaths annually. It is the most common maternal morbidity in developed countries and accounts for half of all postpartum mortalities in developing countries. The third stage of labor remains the most dangerous for women to endure. It is the time frame between delivery of the fetus and expulsion of the placenta that more complications arise, the most severe of which is post partum hemorrhaging (PPH). It has been scientifically and clinically proven that an active management of the third stage of labor (AMTSL protocol) prevents PPH up to 65%, but it is the purpose of this review to dissect this protocol and determine if the use of controlled cord traction (CCT) has any significant benefit of reducing PPH.

**Methods:** An exhaustive literature search was conducted using Medline-OVID, CINAHL, EBM Review Multisearch, Web of Science and ClinicalTrials.gov utilizing the following search terms: post partum hemorrhage, controlled cord traction, oxytocin and labor stage third. Relevant articles were assessed for quality using GRADE. A search of ClinicalTrials.gov revealed one currently registered clinical trial, which has not yet been published, as well as a protocol outline for a study that remains in progress.

**Results:** Three studies met inclusion criteria and were included in this systematic review. A prospective randomized controlled trial with 1648 participants demonstrated a significant difference in PPH when the CCT method was utilized, as opposed to a physiological approach. A randomized, controlled, non-inferiority trial with 12 227 women found that the total loss of blood was less in the CCT group, but did not represent a statistically significant margin. The final study was a randomized, controlled, superiority trial with 103 women participating. Again, blood loss was greater in the physiologically controlled group, but the findings were not statistically significant.

**Conclusion:** Controlled cord traction, in combination with a complete AMTSL protocol has been shown to reduce the occurrence and subsequent complications of post partum hemorrhage. More specifically, CCT has been attributed to shorter durations of the third stage of labor, which is linked to significant clinical benefit and reduces a plethora of maternal complications. The advantages of this treatment far outweigh the risks in the setting of post partum hemorrhaging. Further research is needed to underscore this finding in a more definitive manner.

**Keywords:** Controlled cord traction, third stage of labor, human, post partum hemorrhage

## Degree Type

Capstone Project

## Degree Name

Master of Science in Physician Assistant Studies

## Keywords

Controlled cord traction, third stage of labor, human, post partum hemorrhage

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**Subject Categories**

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# **Reducing the Occurrence of Postpartum Hemorrhage: Controlled Cord Traction Vs. Physiologic Management During the 3<sup>rd</sup> Stage of Labor**

Darla J. Kneeland



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 10, 2013

Faculty Advisor: James T. Ferguson, MPH, PA-C

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

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## Biography

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Darla Kneeland is a native Oregonian who received her Bachelor of Science degree from Oregon State University in 2005 with a major in Microbiology and minor in Chemistry. During her undergraduate work, she spent time volunteering for Hospice and was awarded the coveted URISC grant for her efforts regarding selenium supplementation in rural populations of China. While finishing her bachelor degree, Darla worked at Oregon Health & Sciences University where she was involved in multiple clinical trials. She went on to accept a full-time position with OHSU as the Clinical Trials Coordinator for the Department of Neurological Surgery, exposing her to the Physician Assistant (PA) profession. After encouragement from her family and neurosurgery mentors, she applied to and was accepted into Pacific University's PA program. Her career interests include obstetrics, family medicine, emergency medicine and continued international health care advocacy and education.

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# Abstract

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**Conclusion:** Controlled cord traction, in combination with a complete AMTSL protocol has been shown to reduce the occurrence and subsequent complications of post partum hemorrhage. More specifically, CCT has been attributed to shorter durations of the third stage of labor, which is linked to significant clinical benefit and reduces a plethora of maternal complications. The advantages of this treatment far outweigh the risks in the setting of post partum hemorrhaging. Further research is needed to underscore this finding in a more definitive manner.

**Keywords:** Controlled cord traction, third stage of labor, human, post partum hemorrhage



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To my professors at Pacific University: Thank you for your support, kindness and dedication throughout my time at Pacific. The unfaltering desire to teach and support is what sets this program apart. Thank you again for everything.

To my mom and my family: Words cannot express what your support and dedication to my educational pursuits have meant to me. I would not be where I am today without each of you. To my amazing mom – thank you for being my biggest support and my number one cheerleader. This is for you. I love you a wholla bunch.

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Table I: GRADE Quality of Assessment and Summary of Findings

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## List of Abbreviations

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|       |   |
|-------|---|
| PPH   | Post Partum Hemorrhage  |
| WHO   | World Health Organization   |
| AMTSL | Active Management of the Third Stage of Labor                       |
| CCT   | Controlled Cord Traction  |
| GRADE | Grading of Recommendations, Assessment, Development and Evaluations |
| IM    | Intramuscular Injection   |
| NS    | Normal Saline   |
| RR    | Relative Risk   |
| NNT   | Number Needed to Treat  |
| IV    | Intravenous   |

# **Reducing the Occurrence of Postpartum Hemorrhage: Controlled Cord Traction Vs. Physiologic Management During the 3<sup>rd</sup> Stage of Labor**

## **BACKGROUND**

Post partum hemorrhage (PPH) is a major cause of maternal mortality worldwide; accounting for approximately 100,000 deaths annually.<sup>1</sup> It is the most common maternal morbidity in developed countries and accounts for half of all post partum mortalities in developing countries. PPH, defined as the loss of more than 500 mL of blood after delivery, occurs in up to 18% of births. Blood loss exceeding 1000 mL is considered physiologically significant and can result in hemodynamic instability and subsequent maternal death.<sup>2</sup>

The birth process is divided into three stages. The first encompasses uterine contraction and dilation of the cervix, preparing the body for birth. The second involves actual delivery of the baby, while the third refers to the period between birth and the complete expulsion of the placenta. More women die from complications in the third stage of labor than during the other two stages combined, with the primary cause of death being PPH.<sup>3</sup> International health organizations, such as the World Health Organization (WHO), recommend active management of the third stage of labor (AMTSL) as opposed to a physiologic or 'hands-off' approach, in efforts to reduce the occurrence of PPH. Currently, the definition of AMSTL combines the administration of uterotonic agents, (most commonly oxytocin), late umbilical cord clamping, uterine massage and controlled cord traction (CCT).<sup>4</sup> Studies have shown that AMSTL reduces the incidence of PPH by approximately 65% as compared with physiologic management. Despite the beneficial effects of AMTSL overall, it is important to further assess the effects of its individual components in order to utilize the simplest and most effective intervention.<sup>5</sup>

Controlled cord traction was introduced to obstetric practice by Brandt and Andrews via the Brandt-Andrews maneuver, which consists of elevating the uterus suprapubically while maintaining steady traction on the cord.<sup>6</sup> This procedure has the potential to be clinically important, as it offers birthing attendants and obstetricians a cost-effective tool for managing PPH without involving a medication that introduces harmful side effects and complications. Moreover, in countries where additional uterotonic agents are unavailable, CCT could prove to be the difference between maternal life and death. Will the addition of controlled cord traction as compared to a physiologic approach reduce the occurrence of postpartum hemorrhaging during the third stage of labor?

## **METHODS**

An exhaustive literature search was conducted using Medline-OVID, CINAHL, EBM Review Multisource, Web of Science and ClinicalTrials.gov utilizing the following search terms: post partum hemorrhage, controlled cord traction, oxytocin and labor stage third. The search was narrowed to include English-language literature, human studies and studies with data involving controlled cord traction. The reference sections of each article were explored further for additional relevant sources. Quality assessment was completed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).<sup>7</sup>

## **RESULTS**

Using the search terms described in the previous section, the initial search yielded eight articles for review. After screening relevant articles for human studies and specific use of controlled cord traction, three articles remained.<sup>3,8,9</sup> These included a prospective

randomized control trial,<sup>3</sup> a randomized non-inferiority controlled trial<sup>8</sup> and a randomized controlled superiority trial<sup>9</sup> (See Table I). In addition, a search of ClinicalTrials.gov revealed one currently registered clinical trial,<sup>10</sup> which has not yet been published, as well as a protocol outline for a study<sup>11</sup> that remains in progress.

### **Khan et al**

This prospective randomized control trial<sup>3</sup> compared the use of controlled cord traction with a minimal intervention technique for delivery of the placenta in relation to PPH. This study occurred over six months at Comiche Hospital in Abu Dhabi. Post partum hemorrhage, defined as blood loss of equal to or greater than 500 ml, was the primary outcome. Secondary outcomes included the incidence of retained placenta and the need for additional uterotonic agents to control PPH.<sup>3</sup>

A total of 1648 women who underwent vaginal deliveries were randomly allocated to either the CCT group ( n= 827) or the minimal intervention group (n=821). All patients who were expected to deliver vaginally were eligible to enter this trial. The principal exclusion criterion was the need for emergent cesarean section during labor. Randomization took place at the labor ward, where women who were expected to deliver vaginally were assigned a numbered, sealed and opaque envelope containing instructions for CCT or minimal intervention. Prior to delivery, the envelope was opened by the midwife or obstetrician. All patients for whom an envelope was opened were considered enrolled and follow up was maintained, regardless of the outcome.<sup>3</sup>

Treatment groups were comparable in regards to parity, gestational age, labor induction, hypertension in pregnancy, multifetal gestation, polyhydramnios, vaginal breech delivery and history of retained placenta or PPH. In addition, treatment groups were also

similar in terms of spontaneous delivery, forceps or vacuum delivery, median duration of first and second stages of labor and frequency of episiotomies or tears.<sup>3</sup>

In the CCT group, women received 10 units of oxytocin via intramuscular (IM) injection with delivery of the baby's anterior shoulder, after which the placenta was delivered actively via controlled cord traction utilizing the Brandt-Andrews method. Women allocated to the minimal intervention group delivered their placenta physiologically via maternal expulsive efforts. Continuous intravenous (IV) oxytocin in 10 units in 500 mL of normal saline was administered after delivery of the placenta. Blood was collected by the birth attendant or obstetrician, who used a graduated container to measure blood and blood clots, in addition to weighing soiled linen. A second birth attendant, who was blinded to the study and who was not involved in the birth, was responsible for confirming the amount of blood loss.<sup>3</sup>

Utilization of controlled cord traction for the management of the third stage of labor significantly lowered the overall incidence of PPH as compared with the minimal intervention method (5.8% vs. 11%, respectively, RR 0.53, 95% CI 0.34-0.73, NNT = 20). Moreover, the incidence of retained placenta, defined as greater than 30 min, was also significantly reduced in the CCT group (1.6% vs. 4.5%, OR 0.31, 95% CI 0.15-0.63, RR 0.36, NNT = 35). Women whose deliveries were managed via CCT had a significantly shorter third stage of labor (4 minutes vs. 14 minutes). Lastly, patients randomized to the minimal intervention group required additional uterotonic agents to control PPH (5.1% vs. 2.3%, OR 0.44, 95% CI 0.24-0.78, RR 0.45, NNT = 36).<sup>3</sup>

The authors found that a limitation to this study was the time frame associated with the administration of oxytocin. Women in the CCT group were given IM oxytocin immediately after expulsion of the baby's anterior shoulder, while women in the minimal

intervention group were given oxytocin IV after physiologic expulsion of the placenta. Although this study demonstrated that CCT reduced the occurrence of PPH, it remains unclear which portion of the CCT method was responsible for this benefit. A major drawback of the CCT method is the concern of administering IM oxytocin prior to delivery of the placenta in a woman with undiagnosed multifetal gestation. To avoid this, all patients received prenatal care and underwent routine ultrasonographic examinations. In reference to the previously mentioned data, the authors recommend the use of CCT in management of the third stage of labor and subsequent prevention of PPH.<sup>3</sup>

### **Gulmezoglu et al**

This multicenter, randomized, controlled, non-inferiority trial<sup>8</sup> took place over 15 months, spanning 16 hospitals and two primary care centers in Argentina, Egypt, India, Kenya, the Philippines, South Africa, Thailand and Uganda. The author's goal was to assess whether CCT can be omitted from the active management protocol of the third stage of labor without increasing the risk of severe hemorrhage. Blood loss of 1000 ml or more was the primary outcome while secondary outcomes included additional use of uterotonic agents, need for blood transfusions, manual removal of the placenta, duration of the third stage of labor and maternal death.<sup>8</sup>

A total of 24 390 women were randomized for this study with 11 861 women entering into the simplified AMTSL group and 11 820 women entering into the full AMTSL group. All women who were expected to deliver vaginally were potentially eligible. Exclusion criteria consisted of obstetric emergency requiring cesarean section, mental disorder or distress, minors without a guardian or multifetal gestation. In addition, the fetus had to be at a gestational age of viability according to the corresponding clinical site



regulations. Random allocation took place as close to the anticipated delivery date as possible and was computer generated from a central location; however, neither the investigators nor the participants could be blinded to the interventions or outcomes. If the computer system failed, the allocation was completed using sealed opaque envelopes.

Treatment groups were balanced in terms of age, primigravidae status, duration of gestation, incidence of induced or augmented labor, spontaneous cephalic vaginal delivery and occurrence of episiotomies and tears. In both groups, 10 units of IM oxytocin were administered within one minute following birth. Women allocated to the simplified package delivered their placenta with the aid of gravity and maternal effort and, following signs of placental separation, were encouraged by birth attendants to cough or push in efforts to complete the task. Full package management consisted of CCT (Brandt-Andrews method) applied immediately after observation of a uterine contraction.<sup>8</sup>

The primary outcome was severe post partum hemorrhage, defined as blood loss of 1000 ml or more in one hour and up to two hours for women who continued to bleed past the one hour mark. Collection of lost blood was initiated immediately after birth by passing a drape under the woman's buttocks. Blood was then funneled from the drape into a bucket and weighted on a digital scale together with the soiled drape. The weight of the drape was then subtracted from the equation and converted into milliliters by dividing the value in grams by 1.06 (blood density in g/mL).<sup>8</sup>

The goal of this study was to compare the simplified package to the full package in terms of efficacy within a pre-stated non-inferiority margin. The authors chose this margin by examining the effect of the full package compared with the simplified package in previous trials from published and unpublished data of WHO studies in which post partum blood loss was measured. According to this data, the authors assumed a 1.5% risk of severe

hemorrhage related to utilization of the full package. The non-inferiority margin for the risk ratio was 1.3.<sup>8</sup>

Although the hypothesis of non-inferiority was not met, omission of controlled cord traction has very little effect on the risk of severe hemorrhage (RR 1.07, 95% CI 0.91-1.31, NNT = 500). Women receiving the simplified package demonstrated similar results (RR 1.09, 95% CI 0.91-1.31). However, length of the third stage of labor was reduced by 50% if the full package protocol was utilized (12.6 minutes as compared to 6.1 minutes); yet all other secondary outcomes remained clinically insignificant.<sup>8</sup>

Results conclude that utilizing CCT as a component of an active management protocol has very little, if any, prevention of PPH. Yet, the authors also recognize that CCT is safe and its use should be implemented in the setting of trained birthing attendants, but that the main component of active management continues to be uterotonic pharmaceuticals.<sup>8</sup>

The authors acknowledged the striking limitation of not conducting this study in a blinded fashion. Therefore the risk for potential performance bias cannot be excluded, possibly reducing the power of this trial. The authors go on to recommend that further research focused on preventing PPH in rural settings where birthing attendants and care facilities are scarce, should be pursued.<sup>8</sup>

### **Althabe et al**

This randomized, controlled, superiority trial<sup>9</sup> was conducted in two hospitals in Uruguay over a span of 21 months. Research was focused on the efficacy of CCT in reducing PPH, as compared to a hands-off approach. Primary outcome was total blood loss during the third stage of labor, while secondary outcomes included length of the third stage of labor and use of additional oxytocin to minimize bleeding.<sup>9</sup>

Women aged 18 years or older with documented single term pregnancies, who were admitted during early labor, less than 6 centimeters dilated, were invited to participate. Exclusion criteria included contraindication to oxytocin, any indication of caesarian delivery and severe complications that required emergency interventions. Randomization and allocation were concealed utilizing a computer-generated sequence at each of the participating hospitals. Allocation was completed using sequentially numbered opaque sealed envelopes. At the time of delivery, the midwife or obstetrician assigned to the delivering mother would open the envelope and communicate the assigned intervention to the birthing attendant.<sup>9</sup>

Randomization took place at both hospitals and a total of 204 women were enrolled with 103 women allocated to the CCT group and 101 women allocated to the hands-off group. Treatment groups were balanced in terms of maternal age, gestation, nulliparous status and occurrence of episiotomy or vaginal tearing. Women in both groups received 10 units of oxytocin IM or IV during delivery of the anterior shoulder within one minute of delivery prior to initiation of the predetermined treatment arm. CCT was conducted in a similar fashion to the previously listed studies, using the Brandt-Andrews technique, which matches the World Health Organization recommendations as well as the International Confederation of Midwives and International Federation of Gynecology and Obstetrics recommendations. The hands-off protocol stated that the women were to deliver the placenta physiologically after signs of uterine separation were observed. Women were encouraged to utilize gravity and expulsive efforts to fully expel the placenta.<sup>9</sup>

Lost blood was collected in a plastic drape specifically designed for this purpose. The drape was placed under the woman's buttocks immediately after delivery and blood was collected for 20 minutes. If the woman was not bleeding, the drape was removed; however,

for women who continued to bleed, collection continued until the bleeding stopped or until the woman was transported to another ward. A blinded and independent birthing attendant was responsible for measuring the collected blood by weighing the drape on an electronic scale.<sup>9</sup>

Controlled cord traction utilization during AMTSL may reduce PPH blood loss as compared with a hands-off approach. Median blood loss in the CCT group was 282.0 mL as compared to 310.2 mL in the hands-off group, yet the difference in blood loss (28.2 mL) was not statistically significant (RR 0.14, NNT = 7). However, the third stage of labor was significantly shorter in the CCT group than the hands-off group with a median length of 4.0 minutes as compared to 22.0 minutes, respectively. Of note, the use of additional uterotonic agents was similar between both groups and demonstrated no significant answers to whether or not CCT lowers the need for additional medications to be administered. Results conclude that CCT likely does reduce blood loss during the third stage of labor.<sup>9</sup>

The authors found that the limitations to this study included the inability to blind study participants to the interventions they were receiving. In hopes to minimize any potential bias, study personnel measured blood loss in a standardized way and a third person who was not involved in the study, was responsible for collecting this data. They also discussed the difference in time for placental expulsion in women allocated to the hands-off group. As this time frame included the time taken for complete placental expulsion, rather than placental detachment, the possibility that the longer time period for blood collection resulted in greater blood loss, cannot be excluded. Authors recommend that this potential bias be prevented in future studies by allocating a set time frame in which blood loss should be measured in both groups and support the notion that conducting a larger trial to more adequately determine the efficacy of CCT use should be pursued.<sup>9</sup>

## DISCUSSION

Controlled cord traction as part of an active management protocol for the third stage of labor may reduce the occurrence of post partum blood loss as compared to a physiologic approach. However, it is difficult to state that CCT has much merit in a statistically significant reduction of PPH as opposed to a clinical benefit (See Table I). As previously stated in Khan et al<sup>3</sup> CCT resulted in a profound reduction of PPH, a reduced need for additional uterotonic agents to control blood loss and a significant reduction in the duration of the third stage of labor as well as occurrence of retained placenta. The use of uterotonic agents has widely been accepted as the first line of defense against PPH and all protocols involving the active management of the third stage of labor should include the use of these medications. This point is underscored in Gulmezoglu et al<sup>8</sup> as they state that the most important component of the active management protocol is the uterotonic agent, and, in particular, the uterotonic agent should be used in settings in which the full package cannot be executed safely.<sup>8</sup>

While the studies continue to demonstrate the importance of utilizing an active approach to the management of the third stage of labor, emphasis is needed on the individual components of this approach. Aside from the scientifically proven benefit of uterotonic agents, focus on other manipulations and procedures is needed, thus an analysis of CCT. As stated in Gulmezoglu et al<sup>8</sup> controlled cord traction is safe and its use can be continued in settings in which it is routinely practiced. In addition, use of oxytocin and CCT should be preferred especially if the shortest possible third-stage duration is desirable. Instruction and mastery of the CCT technique should continue in the midwifery and obstetric curriculum.

All three studies<sup>3,8,9</sup> demonstrated a significant reduction in the duration of the third stage of labor. This is critically valuable due to the fact that an increase in time needed for

placental expulsion also increases the likelihood of placental retainment. Furthermore, the actual amount of blood loss depends on the time between placental separation and the contractions of the placental bed by uterine activity. A separated, but not expelled placenta may be accompanied by numerous clots or retroplacental bleeding, culminating in a heavy total blood loss.<sup>4</sup> It is therefore understood that rapid removal of the placenta, following placental detachment, is desirable to prevent unnecessary blood loss and complications.

While the studies<sup>3,8,9</sup> demonstrated that CCT is ultimately safe and mildly effective at reducing PPH, they all have limitations. In the Khan et al<sup>3</sup> study timing of oxytocin administration may have played a role in the results of the primary outcome of blood loss. It is unclear whether the reduction of PPH seen in the CCT group was solely based on the physical procedure of applying Brandt-Andrews traction or if it was based on the administration of oxytocin directly after delivery of the anterior shoulder. It has been recommended in future research to administer oxytocin in a standardized manner to both the control and experimental arms, in hopes to prevent potentially skewed data. The Althabe et al<sup>9</sup> study recognize that blood loss may have been greater in the hands-off treatment arm, secondary to the fact that awaiting complete placental expulsion as opposed to placental separation could lead to increased time for blood collection, attributing to the higher numbers of total blood loss. The authors recommended that a standardized amount of time be designated for blood collection in both treatment arms to prevent future discrepancies.<sup>9</sup>

This issue of an unblinded investigational team and research personnel was the major limitation associated with the Gulmezoglu et al<sup>8</sup> trial. Therefore, potential performance bias as well as selection bias cannot be excluded. In addition, this study based their findings on a pre-selected inferiority calculation as opposed to analyzing raw numbers associated with blood loss. This method of analysis has the potential of downplaying the actual amount of

blood loss, in an attempt to debunk the CCT technique. It is interesting to note that total blood loss between the 500 ml and 1000 ml mark (which was not included as the primary outcome of this study) was in favor of the CCT group with PPH occurring in 13% as opposed to 14% in the simplified group. Despite these limitations, the authors agree that CCT is safe and does not pose any increased harm if the practitioner decides to implement this procedure as part of an AMTSL protocol.

## **CONCLUSION**

Controlled cord traction, in combination with a complete AMTSL protocol has been shown to reduce the occurrence and subsequent complications of post partum hemorrhage. More specifically, CCT has been attributed to shorter durations of the third stage of labor, which is linked to significant clinical benefit and reduces a plethora of maternal complications. The advantages of this treatment far outweigh the risks in the setting of post partum hemorrhaging. The overall combined quality of the studies reviewed is moderate based on the GRADE criteria. It is also important to note that proper training and education concerning the use and practice of CCT has the potential of saving maternal lives in the third world setting, where access to additional uterotonic agents and continuous infusion are either not possible, or unlikely. The practice of CCT offers a safe and simple step that does not require the use of additional medications or equipment, making it a cost-effective safeguard to the prevention of PPH. Further randomized controlled studies designed to reduce previously noted limitations are needed to address this topic further, and promote CCT as a scientifically and clinically respected component of the AMTSL protocol.

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Table I: GRADE Quality of Assessment and Summary of Findings

| Quality Assessment                                     |  |                                     |                          |                        |                                      |                          | Summary of Findings           |                    |                                 |                 |            |          | Importance |
|--|--|-------------------------------------|--------------------------|------------------------|--------------------------------------|--------------------------|-------------------------------|--------------------|---------------------------------|-----------------|------------|----------|------------|
|  |  | Downgrade Criteria                  |                          |                        |                                      |                          |                               | Number of Patients |                                 | Effect          |            | Quality  |            |
| Study  | Design                                   | Limitations                         | Indirectness             | Imprecision            | Inconsistency                        | Publication bias likely  | Study                         | Treatment (total)  | Placebo or no treatment (total) | Relative Risk   | NNT        |          |            |
| Blood Loss (Over 500 ml)                               |  |                                     |                          |                        |                                      |                          |                               |                    |                                 |                 |            |          |            |
| Khan et al <sup>3</sup>                                | Prospective Randomized Control Trial     | No serious limitations              | No serious indirecttness | No serious imprecision | Serious inconsistencies <sup>a</sup> | No bias likely           | Khan et al <sup>3</sup>       | 1648               | 821                             | 0.53            | 20         | Moderate | Important  |
| Gulmezogl u et al <sup>8</sup>                         | Randomized Non-Inferiority Control Trial | One serious limitation <sup>1</sup> | No Serious indirecttness | No Serious imprecision | No serious inconsistencies           | Bias likely <sup>b</sup> | Gulmezoglu et al <sup>8</sup> | 11621              | 239                             | 1.07            | 500        | Moderate | Important  |
| Althabe et al <sup>9</sup>                             | Randomized Superiority Trial             | No serious limitations              | No serious indirecttness | No serious imprecision | Serious inconsistencies <sup>c</sup> | No bias likely           | Althabe et al <sup>9</sup>    | 204                | 101                             | 0.14            | 7          | Moderate | Important  |
| Duration of 3 <sup>rd</sup> Stage of Labor, in Minutes |  |                                     |                          |                        |                                      |                          |                               |                    |                                 |                 |            |          |            |
|  |  |                                     |                          |                        |                                      |                          |                               |                    |                                 | Effect          |            | Quality  | Importance |
|  |  |                                     |                          |                        |                                      |                          |                               |                    |                                 | Treatment group | Time (Min) |          |            |
| Khan et al <sup>3</sup>                                | Prospective Randomized Control Trial     | No serious Limitations              | No Serious Limitations   | No Serious Imprecision | Serious <sup>a</sup> Inconsistencies | No Bias Likely           | Khan et al <sup>3</sup>       | 1648               | 821                             | CCT             | 4          | Moderate | Important  |
|  |  |                                     |                          |                        |                                      |                          |                               |                    |                                 | Physiologic     | 14         |          |            |
| Gulmezogl u et al <sup>8</sup>                         | Randomized Non-Inferiority Control Trial | serious limitation <sup>1</sup>     | No Serious indirecttness | No Serious imprecision | No serious inconsistencies           | Bias likely <sup>b</sup> | Gulmezoglu et al <sup>8</sup> | 11621              | 239                             | CCT             | 6.1        | Moderate | Important  |
|  |  |                                     |                          |                        |                                      |                          |                               |                    |                                 | Physiologic     | 12.6       |          |            |
| Althabe et al <sup>9</sup>                             | Randomized Superiority Trial             | No serious limitations              | No serious indirecttness | No serious imprecision | Serious inconsistencies <sup>c</sup> | No bias likely           | Althabe et al <sup>9</sup>    | 204                | 101                             | CCT             | 4          | Moderate | Important  |
|  |  |                                     |                          |                        |                                      |                          |                               |                    |                                 | Physiologic     | 22         |          |            |

<sup>a</sup> The time frame of oxytocin administration was not equal for both study arms. It is unclear whether or not this difference played a role in the reduction of PPH.

<sup>b</sup> The study investigators as well as personnel were not blinded, so it is impossible to rule out performance bias as well as selection bias.

<sup>c</sup> Additional time was allotted for blood collection in the physiologic group as opposed to the CCT group, so it is impossible to know if this factor attributed to greater blood loss.

